PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	HIV and other STIs self-testing to reduce risk compensation among men who have sex with men who use oral pre-exposure prophylaxis in China: Protocol for a randomised waitlist-controlled trial
AUTHORS	Zhang, Jing; Shang, Hong; Huang, Xiaojie; Chen, Yaokai; Wang, Hui; Zhang, Yonghui; Wang, Hongyi; Mei, Zhu; Jia, Yueru; Chu, ZhenXing; Hu, Qing-hai; He, Xiaoqing; Zhang, Lukun; Hu, Zhili; Bao, Rantong; Li, Shangcao; Ding, Haibo; Jiang, Yongjun; Geng, Wenqing; Tang, Weiming; Xu, Junjie

VERSION 1 – REVIEW

REVIEWER	Jason Ong Monash University, Australia
REVIEW RETURNED	22-Dec-2019

GENERAL COMMENTS	Thank you for the opportunity to review your interesting and important research. A few comments to help strengthen your paper. MINOR COMMENTS - Line 46 - I am curious why you are only testing for HSV2 - why not HSV1 too? (which is now the more common cause of genital herpes than HSV2 in many parts of the world) - Related to the above, could you comment on the reliability of HSV serology? Many places have stopped using HSV serology due to its poor sensitivity/specificity. - This might be due to funding - but you should probably add something in your limitations as to why you are not testing for other STIs like chlamydia and gonorrhoea. - Line 60 - what is the rationale for frequent HBV/HCV testing? - in your study - someone could potentially test for this monthly? What if they are already vaccinated against Hep B? What would be the rationale in frequent testing of HBV? Seems that the resources could be better directed elsewhere e.g. testing for Ct/Ng instead of unnecessary hepatitis screening. - Line 82 - can you clarify if this is for MSM living in China? - Grammatical errors - Line 84, 106-108, 111 - Line 109 - could you define STI self-testing earlier than this - presumably you mean syphilis, HCV/HBV - Line 110 - not sure what is meant by "limited disadvantages" - Line 168 - could you clarify how men will get the kits? postal service? pick-up from a facility? - Line 176 - Tencent - Line 191 - so study participants have to be ambivalent towards using daily vs. on-demand PrEP? how will you track whether men

	have switched themselves from their assigned group and how will you account for this in your analyses? - Line 195 - how? will they get extra messages sent to their WeChat/SMS? or only encouraged during the study visits? - Line 203 - what is someone already had past treated syphilis - presumably this test they use will always be positive? What are these men told regarding the syphilis part of the test? do they always have to come back for confirmatory testing? - Line 219 - is testing and treatment free? - Line 222 - is the support line available 24 hour, 7 days a week or only during office hours? I am thinking that men may choose to test outside usual office hours and what type of support would they receive for those times? - Line 257 - severe - Line 294 - which diagnostic are you using for HSV? - Line 333 - why is this exactly 23.1%? - In general, all abbreviations should be defined at first mention e.g. CBO, IRB, etc... - Figure 1 - so in each arm - there will be 250 who will take daily PrEP and 250 who are on-demand PrEP?

REVIEWER	Curtis Chan The Kirby Institute UNSW, Australia
REVIEW RETURNED	03-Mar-2020

GENERAL COMMENTS	Protocol is clearly defined. This paper would benefit greatly from additional proofreading. Introduction Clear background and rationale with evidence. - Would be useful to make clear that risk compensation here refers to risk compensation of STIs other than HIV. As PrEP is efficacious in HIV prevention, increased rates of CAI should not impact on the relative risk of HIV infection. However, as discussed, this is not true of STIs so this point can be emphasised more. Clear hypotheses, objectives are made clearer in the study aims section. Method: Participants, interventions and outcomes Clear description of study settings and list of countries where data will be collected. There does not appear to be a reference to where list of study sites can be found Clear inclusion criteria. Brief description of exclusion criteria for the CROPrEP trial would be useful. Outcomes are outlined. Instead of suggesting “whether HIV and other STIs self-testing kits can decrease the frequency…”, it may be more prudent to say whether it will affect the frequency (either increase, decrease or no change). Participant timeline is clear from study flowchart in figure 1 Sample size calculations are clear. There does not appear to be strategies for recruitment to reach target sample size. Method: Assignment of interventions Sequence generation, concealment mechanism, blinding and allocation implementation is clear. Method: Data collection, management and analysis Data collection plan is clear. There does not appear to be mention of retention strategies, such as reminders for completing follow-up visits and surveys. Data management strategies are mentioned from downloading from a larger database. There does not appear to be mentions of further quality checks (e.g. range checks).

	Statistical methods are clearly outlined. There does not appear to be mention of how missing data will be handled at the analysis phase. Method: Monitoring An independent data inspection company will be employed to verify the quality control of the coordinating centre. Reporting structure are outlined. There are clear directions for the interim analysis, who has access to interim data and termination of the trial. Harms and adverse effects will be recorded by clinical physicals. Further guidelines on the assessment of those adverse effects would be helpful. Ethics and dissemination Study protocol has received ethic approval from IRB. No mention of process of potential protocol amendments. Consent, confidentiality, declaration of interests and access to data are clear. Dissemination of results to relevant parties are not mentioned in this protocol. Authorship or public access to full protocol/participant level dataset are also not mentioned Minor This manuscript would benefit greatly from further proofreading. Not a complete list of potential editorial problems Line 84 “but are also highly acceptable and feasible among PrEP users” or “but also have high acceptability and feasibility among PrEP users” Line 99 “PrEP decreases users’ risk” or “PrEP decreases the user’s risk” Line 104, starting sentence with And – probably better with “Furthermore” or dropped completely Line 106 “the incidence of syphilis among MSM taking PrEP is 44.6 times higher than MSM not taking PrEP Line 111 “combined with HIV and other STIs is lacking” Line 112 starting sentence with And Line 115 “the PrEP programs in China are still in…” Line 138 “counselling and testing (VCT) rooms” – I’m unsure if this was intended to be plural Line 208 Typo with a space and a period “. .” Line 176 and Line 213: “study sites’” or “study site’s” – inconsistent. Should be sites’ for both Line 254 starting sentence with And Line 257 Severe adverse events Line 258 72 hours Line 270 “confidentiality contract” is likely to be more accurate

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Jason Ong

Institution and Country: Monash University, Australia

Please state any competing interests or state ‘None declared’.

Please leave your comments for the authors below

Thank you for the opportunity to review your interesting and important research. A few comments to help strengthen your paper.

MINOR COMMENTS

- Line 46 - I am curious why you are only testing for HSV2 - why not HSV1 too? (which is now the more common cause of genital herpes than HSV2 in many parts of the world)

Thank you for the comments. Testing both HSV-1 and HSV-2 will definitely be a better idea. But due to the following reasons, we prioritized the limited resources of this trial on the testing of HSV-2. But we will definitely seize a chance on study of HSV-1 among MSM in China in the future.

a. *Genital herpes may be caused by either herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) but, globally, the large majority of cases are caused by HSV-2 [1]. Data since late 1990s demonstrated a shift towards HSV-1 in developed regions such as the UK, USA and Europe. However, according to a recently published study, describing the temporal trends of HSV-1 and HSV-2 over the past 14 years in Australia, the proportion of first episode of anogenital herpes due to HSV-1 increased significantly over time in women and heterosexual men but not in MSM [2]. To our knowledge, there is no data for prevalence of HSV-1 infection among MSM in China to prove a necessity of conducting HSV-1 test in this study [3].*

b. *Meanwhile, HSV-2 has significant impact on HIV acquisition, transmission and progression. As in PrEP study, HSV-2 is a biomarker for risk of HIV seroconversion. According to previous study, the association between HSV-2 and HIV increased strongly during the HIV epidemic, while the association of HIV and HSV-1 remained stable [4]. The association of HSV-2 infection and HIV sero-conversion are widely observed among MSM in China [5-7]. The prevalence of HSV-2 infection among MSM in China is 10.6% (6.2-17.6%)[8]. Previous RCT study also revealed that PrEP reduces acquisition of HSV-2 among heterosexual men and women [9]. Above evidences support the decision to include HSV-2 testing in this study.*

- Related to the above, could you comment on the reliability of HSV serology? Many places have stopped using HSV serology due to its poor sensitivity/specificity.

According to published data, the sensitivity of the serology assay for HSV-2 is high and the specificity is relatively low[10]. False positive HSV-2 results can happen, especially in people who are at low risk for herpes infection. But among MSM in China, the prevalence of HSV-2 infection is around 10.0% [8]. The positive result of IgG of HSV-2 represents the individual has once infected with HSV-2; while we also test IgM of HSV-2, which can distinguish whether it is a current infection of HSV-2 or not. All the laboratory-based tests in this trial are conducted in licensed laboratories affiliated to the study sites,

which are all high ranked general hospitals. Quality control and reference for each test has been performed at each of the four study sites before participant enrolment and during the study.

- This might be due to funding - but you should probably add something in your limitations as to why you are not testing for other STIs like chlamydia and gonorrhoea.

Thank you very much. We have added this as a limitation in Line 387-395 as a major limitation of this study as follow:

As a major limitation, this study only detects limited types of STIs other than HIV, which not including Chlamydia trachomatis and Neisseria gonorrhoeae (CT/NG) and other STIs. Previous studies show that the infection rate of CT / NG among general MSM population in China is low [11] [12], compared to syphilis. But the detection for CT/NG is relatively expensive. In order to accurately assess the infection rate of CT/NT, each MSM needs to be sampled and tested for three anatomical sites including the oropharyngeal site, urethral, and anorectal site [13]. The average cost of sample and testing of CT / NG at each anatomical site is more than 15 US dollars. This project group could not afford this cost. Therefore, no CT/NG testing were carried out in this study. It is strongly recommended to perform relevant STI testing in the future study.

- Line 60 - what is the rationale for frequent HBV/HCV testing? - in your study - someone could potentially test for this monthly? What if they are already vaccinated against Hep B? What would be the rationale in frequent testing of HBV? Seems that the resources could be better directed elsewhere e.g. testing for Ct/Ng instead of unnecessary hepatitis screening.

The self-reported rate of HBV vaccination among participants at enrollment of this study is 29.0%. In China, hepatitis B vaccination for adult has not been systematically performed [14]. China has begun incorporated vaccine for hepatitis B into the national planned immunization in 1992, requiring all newborns to be vaccinated against hepatitis B, but the costs of the vaccination and medical service are paid by the parents. In 2002, the hepatitis B vaccine was officially included into the free planned immunization, the vaccine became free but the parents still need to pay for the medical service. Most of the MSM participants in this study were born before 2002, and even before 1992. Most of them were not benefit from the free national planned vaccinated against HBV.

The study drug, Truvada produced by Gilead, is used as PrEP and also has the treating effect of HBV. According to the instruction of Truvada, HBV must be regularly tested for the users. If the participants have HBV sero-conversion during follow-up, it is necessary to closely monitor their PrEP medication compliance. Because poor medication compliance may cause HBV disease worsen. Given the large burden and high incidence rate of HBV among adults in China, especially among those aged 30–50 years old [15], we conducted the frequent HBV testing.

The self-testing kits used in this study is a four-in-one testing kits combined with testing kits of HIV, syphilis, HBV and HCV. Also, the laboratory-based testing of HBV and HCV are relatively cheap and do not require expensive testing equipment.

As for HCV, which is mainly transmitted by blood transfusion, acupuncture, and intravenous drug use, it is extremely harmful to the health and life of patients. MSM is a key population impacted by HCV infections. China has the world's largest burden of hepatitis C and related liver disease. Although

Lower HCV seroprevalence (<1%) was found among MSM in China [16], there has been an high and increasing incidence of HCV among PrEP users reported in several trial worldwide [17, 18]. HIV-negative MSM using PrEP are at risk of incident HCV infection. Therefore, we choose this four-in-one testing kits including HCV testing.

- Line 82 - can you clarify if this is for MSM living in China?

No, the PrEP users mentioned were individuals, men who have sex with men, transgender individuals, and heterosexual men and women, assessed for comprehensive HIV prevention services at a large urban academic medical center in northern Manhattan between January 1, 2015, and November 30, 2017.

We have clarified this, currently in Line 78-80.

- Grammatical errors - Line 84, 106-108, 111

Thank you so much. I have corrected the errors. They are currently in Line 82, 104, 109.

- Line 109 - could you define STI self-testing earlier than this - presumably you mean syphilis, HCV/HBV

Yes, I have revised accordingly, currently in Line 97-98.

- Line 110 - not sure what is meant by "limited disadvantages"

The original article is "Self-testing may increase first-time testing and has limited harms"，which indicates pressured testing, violence and coercion after testing.

This has been deleted now.

- Line 168 - could you clarify how men will get the kits? postal service? pick-up from a facility?

Participants get the kits from pick-up at the study sites. They can also get the kits from postal service if it is necessary. For example, we mailed out HIVST to participants during the quarantine of COVID-19 pandemic, since they can't attend to the clinical visits.

I have now clarified that "The immediate HIV and STI self-testing arm will immediately receive free HIV from pick-up at the study site (postal service is also available if necessary)" in Line 169-170.

- Line 176 – Tencent

Thank you so much. I have corrected it, currently in Line 179.

- Line 191 - so study participants have to be ambivalent towards using daily vs. on-demand PrEP? how will you track whether men have switched themselves from their assigned group and how will you account for this in your analyses?

At enrollment, participants have to choose between daily and on-demand PrEP. While, during the follow-up, the number of sexual partners of participants may increase or decreased or participants may find the PrEP regimens they chose does not suit their life. Therefore, they can switch their PrEP regimens. This switch was widely observed and reported in previous trials [19].

At each quarterly follow-ups, the investigators will track the switch of regimen via physician-administrated consultation, self-reporting from participants , and pill counting.

As for analyses, the primary outcomes are the impact of HIVST usage on the occurrence of CAI, number of sexual partners, and incidence of STIs during follow-up. We will describe the rate of switch of regimen in participants and analyze it as a covariate in multivariable analysis if necessary.

- Line 195 - how? will they get extra messages sent to their WeChat/SMS? or only encouraged during the study visits?

Participants allocated in the intervention group received oral and written instruction of HIVST from staffs before they leave with the kits. During this instruction, they are told that they can not only use it to test themselves, but also encouraged to share and use it to test their male sexual partners. At the time of quarterly follow-up, the investigator also encourages participants to utilize HIVST kits.

- Line 203 - what is someone already had past treated syphilis - presumably this test they use will always be positive? What are these men told regarding the syphilis part of the test? do they always have to come back for confirmatory testing?

The history of diagnosis of STIs was also collected at enrollment and follow-ups. If someone self-reports that he has already known and has treated syphilis, physicians will instruct him about the possible result of syphilis self-testing. They don't need to come back to the study site for confirmatory testing repeatedly.

- Line 219 - is testing and treatment free?

No, it's not.

- Line 222 - is the support line available 24 hour, 7 days a week or only during office hours? I am thinking that men may choose to test outside usual office hours and what type of support would they receive for those times?

The WeChat account was set up with the automatic response menu with frequent asked questions, which is 24 hour, 7 days. The telephone support line works from 8 am to 12 pm.

We have added this in Line 229-231.

- Line 257 – severe

Thank you so much. I have corrected it.

- Line 294 - which diagnostic are you using for HSV?

HSV-2 infection was determined by HSV-2-specific immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody testing using an ELISA (Beier Bioengineering, Beijing, China).

I have added this information on Line 312-314.

- Line 333 - why is this exactly 23.1%?

Thank you for pointing out this mistake. This was 30.0% in the previous version. The mistake must happen during polishing. I have corrected it to 30.0% now, and also checked for other potential mistake of this kind.

- In general, all abbreviations should be defined at first mention e.g. CBO, IRB, etc...

Yes, I have defined CBO at first mention in Line 140. And I have added the definition of IRB in Line 266.

- Figure 1 - so in each arm - there will be 250 who will take daily PrEP and 250 who are on-demand PrEP?

Yes.

Reviewer: 2

Reviewer Name: Curtis Chan

Institution and Country: The Kirby Institute UNSW, Australia

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Protocol is clearly defined. This paper would benefit greatly from additional proofreading. Please see attached document for further comments

Introduction

Clear background and rationale with evidence.

- Would be useful to make clear that risk compensation here refers to risk compensation of

STIs other than HIV. As PrEP is efficacious in HIV prevention, increased rates of CAI should

not impact on the relative risk of HIV infection. However, as discussed, this is not true of STIs so this point can be emphasised more.

Thank you so much. I have emphasized on this in Line 86.

Clear hypotheses, objectives are made clearer in the study aims section.

Thank you.

Method: Participants, interventions and outcomes

Clear description of study settings and list of countries where data will be collected. There does not appear to be a reference to where list of study sites can be found

We have mentioned in Line 130-135 about the study sites as following: "The CROPrEP trial, along with the current trial, is conducted in the following four major cities: Beijing, Shenyang, Chongqing, and Shenzhen (the four study sites are The Youan Hospital of Capital Medical University in Beijing, The First Affiliated Hospital of China Medical University in Shenyang, The Chongqing Public Health Medical Center of Southwest University in Chongqing, and The Third People's Hospital of Shenzhen). These four cities are major cities located in the middle, northeast, southwest and southeast parts of China."

Clear inclusion criteria. Brief description of exclusion criteria for the CROPrEP trial would be useful.

Thank you so much. I have added this in Line 160-164.

Outcomes are outlined. Instead of suggesting "whether HIV and other STIs self-testing kits can decrease the frequency…", it may be more prudent to say whether it will affect the frequency (either increase, decrease or no change).

Yes, I agree. I have revised accordingly in Line 248.

Participant timeline is clear from study flowchart in figure 1

Thank you.

Sample size calculations are clear. There does not appear to be strategies for recruitment to reach target sample size.

The strategies for recruitment to reach target sample size were conducted within the CROPrEP trial, including both online (advertising on public social platforms) and offline methods (clinical based sampling, community-based sampling, venue-based sampling, and peer referrals). I have also mentioned this in Line 176-183.

Method: Assignment of interventions

Sequence generation, concealment mechanism, blinding and allocation implementation is clear.

Thank you.

Method: Data collection, management and analysis

Data collection plan is clear. There does not appear to be mention of retention strategies, such as reminders for completing follow-up visits and surveys.

Thank you for pointing this out. I have added this in Line 184-186, as "During the follow-up period, participants will have access to supports for adherence from physicians and leaders from CBOs providing routine reminders of follow-up visits and survey via shot message, face-to-face appointment, and live chat."

Data management strategies are mentioned from downloading from a larger database. There does not appear to be mentions of further quality checks (e.g. range checks).

Thank you for pointing this out. I have added this in Line 334-335 as "Downloaded data will be exam for distribution and range before analysis."

Statistical methods are clearly outlined. There does not appear to be mention of how missing data will be handled at the analysis phase.

Instead of handling missing data, avoiding occurrence of missing data is easier. We mentioned in Line 280-282 that "The online data collection platform has a built-in quality control system, which will remind the participants and staff before participants submit their survey if there is missing data and cross check for logical mistakes." Other than this online data collection, we have the offline clinical visit record from physicians including crucial variables, such as HIV-related behaviors and symptoms of STIs. If the missing data is about the laboratory testing results, we will trace back to the record from laboratory. If there is still missing data and can't be makeup from any records offline, we will treat it as a separate category by itself, and explain why these data are missing.

Method: Monitoring

An independent data inspection company will be employed to verify the quality control of the coordinating centre. Reporting structure are outlined. There are clear directions for the interim analysis, who has access to interim data and termination of the trial.

Thank you.

Harms and adverse effects will be recorded by clinical physicals. Further guidelines on the assessment of those adverse effects would be helpful.

I have added the following information in Line 260-265: The causal association and severity assessment will be independently evaluated by two physicians. Any reported adverse events will be clinically tracked until they are restored or stabilized. Although according to guideline of HIVST by WHO, instances of harms following voluntary HIV self-testing have been few, we will adapt medical resource to monitor adverse events during follow-up when it occurs. The assessment of adverse effects of PrEP was described in previous published article [20].

Ethics and dissemination

Study protocol has received ethic approval from IRB.

No mention of process of potential protocol amendments.

I have added this in Line 266-267.

Consent, confidentiality, declaration of interests and access to data are clear.

Thank you.

Dissemination of results to relevant parties are not mentioned in this protocol. Authorship or public access to full protocol/participant level dataset are also not mentioned

I have added this in the method section under the subtitle of "Patient and public involvement".

Minor

This manuscript would benefit greatly from further proofreading. Not a complete list of potential editorial problems

Thank you so much! I have corrected following mistake accordingly, and have proofread.

Line 84 “but **are** also highly acceptable and feasible among PrEP users” or “but also have **high acceptability and feasibility** among PrEP users”

Line 99 “PrEP decreases **users’** risk” or “PrEP decreases the **user’s** risk”

Line 104, starting sentence with And – probably better with “Furthermore” or dropped completely

Line 106 “the incidence of syphilis among MSM taking PrEP **is** 44.6 times **higher than** MSM not taking PrEP

Line 111 “combined with HIV and other STIs is **lacking**”

Line 112 starting sentence with And

Line 115 “the PrEP programs in China **are** still in…”

Line 138 “counselling and testing (VCT) **rooms**” – I’m unsure if this was intended to be plural

Line 208 Typo with a space and a period “. .”

Line 176 and Line 213: “study sites’” or “study site’s” – inconsistent. Should be sites’ for both

Line 254 starting sentence with And

Line 257 **Severe** adverse events

Line 258 72 **hours**

Line 270 “**confidentiality** contract” is likely to be more accurate

References

[1] Genital HSV Infections. Available at https://www.cdc.gov/std/tg2015/herpes.htm. Accessed 8th August. . 2015.

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VERSION 2 – REVIEW

REVIEWER	Jason Ong Monash University
REVIEW RETURNED	17-Apr-2020

GENERAL COMMENTS	Thank you for addressing my comments adequately. I noticed some minor typos and grammatical errors in the new texts. Please review before publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Jason Ong

Institution and Country: Monash University

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thank you for addressing my comments adequately. I noticed some minor typos and grammatical errors in the new texts. Please review before publication.

Thank you very much. We have reviewed and revised minor typos and grammatical errors.